exposure with an estimated risk of 2 percent to 3 percent a year. In the view of most experts, this amount of risk justifies immunization.

The manufacturer recommends antibody testing (hepatitis B surface antibody at $20 per test) before vaccination to eliminate unnecessary and costly injections in people who have naturally acquired immunity. While this is the current standard, its cost effectiveness has been questioned. Clearly the response rate to the vaccine eliminates the need for follow-up antibody studies in all but special circumstances.

What is needed is a low-cost safe method for attacking this global problem. We now have what appears to be a very good beginning.

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Plasmapheresis as Therapy

PLASMAPHERESIS, or plasma exchange, a new and sophisticated form of bloodletting, is rapidly becoming a major therapeutic tool for the treatment of a variety of disease processes. This innovation has been made possible by technologic advances in centrifugation that allow the separation of various cell components from plasma of human blood. About 41,000 such apheresis procedures were done in the United States last year on a minimum of 41 different disease processes. The data base for the entire industry is based on anecdotal reports. Only now are double-blind studies being done to further delineate the indications and to compare the efficacy of this form of treatment with other conservative measures. The one group of diseases wherein the use of plasmapheresis seems to be clearly accepted by all is the hyperviscosity syndromes in which aberrations in blood flow occur as a result of the presence of abnormal blood proteins. Here the procedure is of most value in an acute crisis. Long-term management requires both plasmapheresis and immunosuppressive therapy.

Despite the limited data base, recognized authorities in the field suggest that there is enough information available to justify plasmapheresis in certain clinical settings. In most cases it is assumed that immunologic mediators of disease are removed in the process of plasmapheresis. Besides the hyperviscosity syndromes, plasmapheresis may also be beneficial for the following disorders:

- Myasthenia gravis, especially in patients who have failed to respond to steroids and antimetabolite therapy or in those who are in an acute respiratory crisis.
- Goodpasture's syndrome, biopsy proved or associated with lung hemorrhage, and acute crescentic nephritis that is rapidly progressing and not responding to steroid drugs.
- Lupus nephritis, the classic circulating immune complex disorder. Unfortunately, the criteria for the use of plasmapheresis have not yet evolved in this disorder and double-blind studies are only now under way to exactly define its value.
- Rapidly progressing systemic sclerosis with not only skin but also multiorgan system involvement, though the number of cases so far is extremely small and widespread clinical use probably cannot be justified and should be restricted to academic centers. The same holds true for other rheumatic diseases such as polymyositis and dermatomyositis.

Plasmapheresis is a popular and rapidly expanding area in which only time and additional studies are needed to give this tool its proper place in clinical practice. English physicians have recently suggested that all patients who receive an apheresis procedure should be in a clinical registry so that a maximum amount of information can be obtained regarding this treatment. This should also be done in this country.

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Calcium Channel Blocking Agents in Cardiovascular Medicine

THE CALCIUM CHANNEL blocking agents are a heterogeneous group of compounds that represent a new generation of drugs for the treatment of cardiovascular disease. Their therapeutic actions derive from their capacity to inhibit calcium flux through the "slow" channels of cardiac and smooth muscle cell membranes. The slow channels are so named because cellular entry of calcium is normally delayed during electrical depolarization until the plateau phase of the action potential, in contrast to sodium transmembrane passage through the "fast" channels at the initiation of depolarization. The electrical and contractile functions of cardiac and smooth muscle tissue are dependent on this phasic cellular entry of calcium which activates calcium-dependent adenosine triphosphatase (ATPase), an essential step in excitation-contraction coupling. Skeletal muscle cells, however, have abundant intracellular calcium stores and their activity does not depend on influx of calcium. Therefore, agents that inhibit calcium flux can modulate cardiac and smooth muscle activity, an effect with therapeutic potential in certain conditions.

The cardiovascular effects of the calcium antagonists are the result of their direct and indirect actions on the heart and vasculature at multiple levels. The direct effects of inhibition of calcium transport by these agents are smooth muscle relaxation and thus systemic and coronary vasodilation and negative cardiac inotropy. Depending on the specific drug, these agents either have

negligible actions on cardiac electrophysiologic function or prolong the refractory period of the atrioventricular node and reduce sinoatrial node automaticity. These effects result in reduction of blood pressure, prevention of coronary vasospasm and antiarrhythmic activity in supraventricular tachyarrhythmias. The coronary vasodilating action provides an important mechanism of therapy for coronary vasospastic (Prinzmetal) angina, and lowered blood pressure and negative inotropy favor reduction of myocardial oxygen demand and alleviation of nonvasospastic angina. Reflex sinus tachycardia may occur as a result of vasodilator-induced fall in blood pressure. The modest negative inotropic action may be offset by a reduction of afterload through systemic arterial dilatation, but this is unpredictable. The major adverse effects of the calcium antagonists are extensions of their pharmacologic actions: hypotension, myocardial depression and atrioventricular block.

Three calcium antagonists—verapamil, nifedipine and diltiazem are now available in this country and therapeutic trials have been initiated with more recently developed drugs of this class. All three available agents are vasodilators, though nifedipine is most potent in this regard, and reflex tachycardia due to blood pressure reduction may be significant with this agent. Verapamil and, to a lesser degree, diltiazem produce the inhibitory cardiac electrophysiologic effects enumerated above and nifedipine is devoid of significant, direct cardiac electrophysiologic effects. The Food and Drug Administration (FDA)-approved indications for the use of these agents include coronary vasospastic angina and nonvasospastic angina for all three and, for intravenous verapamil, paroxysmal supraventricular tachyarrhythmias. The calcium blockers have been highly effective in anginal states, alone or in combination with nitrates or β-blockers (or both), in patients in whom the latter drugs have been unsuccessful. These agents are usually used in patients refractory to conventional therapy and can be administered in combination with either nitrates or β-blockers for nonvasospastic angina and with nitrates for vasospastic angina. Although such a combined approach has considerable therapeutic potential, myocardial depression and hypotension are important risks.

Intravenous verapamil has become a first-line agent for the treatment of supraventricular tachyarrhythmias. Current reports indicate that the drug promptly converts paroxysmal supraventricular tachycardia to sinus rhythm in more than 80 percent of patients. Conversion of atrial fibrillation and flutter to sinus rhythm by verapamil administration occurs only occasionally, but in these arrhythmias the drug slows ventricular rate in most patients. Because of its efficacy, intravenous verapamil has had a major impact on the emergency treatment of supraventricular tachyarrhythmias.

The calcium antagonists are associated with side effects in about 10 percent to 15 percent of patients, which can often be managed by decreasing the dosage. Hypotension is the adverse effect of primary concern with intravenous verapamil, which is contraindicated in cases of tachyarrhythmia associated with sinus node dysfunction. Further information is required regarding the clinical pharmacology of these drugs, particularly in relation to drug interactions. In this regard, both nifedipine and verapamil have been reported to raise serum digoxin levels in patients receiving the glycoside.

Current interest in the therapeutic potential of the calcium antagonists, based on their pharmacologic properties, extends to a wide spectrum of cardiovascular conditions. These include hypertrophic obstructive cardiomyopathy, hypertension, congestive heart failure, vasospastic disorders, limitation of myocardial infarct size and myocardial preservation during cardiac operations. The calcium antagonists have already established an important place in the treatment of cardiac disease and their full therapeutic potential has not yet been fully realized.

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Percutaneous Transluminal Coronary Angioplasty

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) is a promising new catheter technique for dilating stenosed coronary arteries with consequent improvement in coronary blood flow and clinical manifestations of myocardial ischemia. Dotter and Judkins first described a similar method for transluminal recanalization of peripheral arterial stenoses in 1964; hemorrhagic and thrombotic complications limited its use, however. In 1973 Grüntzig developed a double-lumen balloon catheter that was first tested in laboratory animals and then applied sequentially in humans to peripheral and renal arteries, cadaver hearts and coronary arteries during aortocoronary bypass surgical procedures. In September 1977 in Zurich the technique was first used during cardiac catheterization. Since then, it has been used increasingly throughout the world in patients with symptomatic coronary atherosclerosis; its proper role and limits in the treatment of this disease remain a focus of intense clinical investigation.

Initially, only those patients who had single-vessel involvement and a lesion that was proximal, discrete, concentric and noncalcified were selected for the procedure. Cardiologists are now beginning to apply the technique to patients who have multivessel disease where all or most lesions appear amenable to dilatation. Lesions situated in or at the anastomosis of a saphenous vein graft have also been dilated successfully. All patients should be candidates for bypass graft operation because in 6 percent to 8 percent of percutaneous transluminal coronary angioplasty procedures a sudden occlusion or deterioration of flow causes impending infarction and immediate surgical intervention is then necessary.